Hepatic Resection for Colorectal Liver Metastases

Influence on Survival of Preoperative Factors and Surgery for Recurrences in 80 Patients

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This report analyses an experience with 80 liver resections for metastatic colorectal carcinoma. Primary colorectal cancers had all been resected. Liver metastases were solitary in 44 patients, multiple in 36 patients, unilobar in 76 patients, and bilobar in 4 patients. Tumor size was less than 5 cm in 33 patients, 5–10 cm in 30 patients, and larger than 10 cm in 17 patients. There were 43 synchronous and 37 metachronous liver metastases with a delay of 2–70 months. The surgical procedures included more major liver resections (55 patients) than wedge resections (25 patients). Portal triad occlusion was used in most cases, and complete vascular exclusion of the liver was performed for resection of the larger tumors. In-hospital mortality rate was 5%. Three- and 5-year survival rates were 40.5% and 24.9%, respectively. None of the analysed criteria: size and number of liver metastases, delay after diagnosis of the primary cancer, Duke's stage, could differentiate long survivors from patients who did not benefit much from liver surgery due to early recurrence. Recurrences were observed in 51 patients during the study, two thirds occurring during the first year after liver surgery. Eight patients had resection of "secondary" metastases after a first liver resection: two patients for extrahepatic recurrences and six patients for liver recurrences. Encouraging results raise the question of how far agressive surgery for liver metastases should go.

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GROWING EVIDENCE SUGGESTS that surgical resection is currently the only efficient treatment for some patients with liver metastases (LM) of colorectal origin. However, it is clear that not all patients benefit from these resections, since early postoperative cancer recurrences are observed in many patients.[1,2]

Detection of clinical factors that could predict the outcome after surgery would improve the selection of patients. Large series should be analyzed to increase our knowledge on the evolution after resection of LM. However, due to the small proportion of resectable metastases, most published series do not exceed 50 patients. Furthermore, for obvious ethical reasons no prospective randomized study comparing resection of LM *versus* no treatment can be undertaken. Consequently, more information must be obtained from retrospective studies of resected LM.

How surgical resection of secondary liver deposits can prolong life in some patients remains unknown. The first attempts at resecting LM were directed toward solitary tumors and then extended to unilobar lesions. Only experience can tell whether this aggressive treatment may now be extended to patients with bilobar nodules or even LM recurring after a first resection. We report an experience with 80 liver resections for metastatic colorectal carcinoma.

Patients and Methods

From May 1970 to December 1985, 80 patients had partial liver resection for metastatic colorectal carcinoma, most of them being operated on in recent years. There were 41 men and 39 women, the mean age being 58.7 years (range: 24–77 years).

All primary tumors were adenocarcinomas located on the colon (right 7, transverse 4, left 31, multiple 3) or the rectum (35). Their local extension, Duke's stage, and histologic degree of differentiation are summarized in Table 1. Little information was available on the primary tumors of six patients operated on in another institution and referred later for the treatment of LM. The procedures performed for the resection of these adenocarcinomas were

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TABLE 1. *Primary Tumors*

	No. of Tumors
Duke's stage	
A	0
B	19
C	55
Unknown	6
Differentiation	
Well	47
Moderate	14
Poor	9
Mucinous	4
Unknown	6
Adjacent organs involved	
Kidney	1
Spleen	1
Bladder	2
Liver	1
Stomach	1
Pancreas	1
Abdominal wall	3
Ovary	1
Uterus	1

colonic or rectal resections with anastomosis in 55 patients, abdominoperineal resections in 18 patients, and Babcock's procedures or coloanal J pouch anastomosis in seven patients.

In 43 patients the diagnosis of the primary cancer and LM were synchronous, and in 37 patients the LM was diagnosed 2–70 months after the primary cancer (median: 23.7 months). Forty-four patients had solitary nodules and 36 patients had multiple metastases separated by normal liver parenchyma. In 14 patients, more than four metastases were resected. In 33 patients, LM measured less than 5 cm, in 30 patients LM measured 5–10 cm, and in 17 patients they were larger than 10 cm.

In 76 patients (Table 2) liver deposits were either unilobar (63 patients) or involved two adjacent lobes that could however be resected with one major liver resection (13 patients). In four patients LM involved both sides of the liver and required two different partial liver resections. In 22 patients the presence of LM was associated with clinical symptoms: pain (13 patients), fever (2 patients), palpable liver mass (7 patients), weight loss of more than

TABLE 2. *Location of Liver Metastases*

	No. of Patients
Right lobe	40
Right and median lobes	13
Median lobe (segment IV)*	4
Left lateral segments	14
Left lobe	5
Right and left lobes	4

* According to Couinaud.

TABLE 3. *Liver Resection*

	No. of Patients
Wedge resection	25
Major resection	55
Right lobectomy (segments V–VIII)*	28
Extended right lobectomy (segments IV–VIII)*	11
Left lobectomy (segments II–IV)*	4
Left lateral segmentectomy (segments II–III)*	9
Median lobectomy (segment IV)*	3

* According to Couinaud.

10% of the body weight (7 patients), and jaundice (2 patients).

The characteristics of the partial liver resections performed are summarized in Table 3. Twenty-five patients had wedge resections for tumors less than 5 cm. In two of these patients, two different nodules were located on the right and on the left lobes and required two separate wedge resections. The other 55 patients had major resections that were associated in two cases with the wedge resection of a different nodule located on the other lobe.

Intestinal and liver resections were performed during the same surgical procedure in 19 patients with easily accessible small synchronous LM. In two patients the LM were discovered 1 and 3 months, respectively, before the primary cancer could be detected and resected. The other 59 patients had liver resection 2–71 months after the intestinal procedure either because the surgeon decided not to perform two major surgical procedures at the same time or because the diagnosis of LM was metachronous.

Six patients had major liver resection for a recurring solitary LM 5–40 months after a first resection, which had been a wedge resection in most cases. Location of the recurrence was on the same lobe than the first LM in three patients and on the other lobe in three patients. In four patients, resection of symptomatic LM was considered to be palliative since gross tumor was left in place. All LM were confirmed by histologic examination; adjacent parenchyma was normal and noncirrhotic in all patients. There was no known extrahepatic involvement at the time of liver resection except in one patient with nonevolutive pelvic recurrence and a symptomatic liver metastase.

After resection, the patients were seen in the clinic at 6-month intervals during the first 2 years and then every year. All patients had a clinical examination, liver ultrasound or abdominal CT scan, and chest roentgenogram during the 6 months before the completion of the study. Follow-up was complete in all patients except one who was known to be alive and disease-free 36 months after liver surgery. Time to recurrence and survival data were estimated and plotted using the actuarial method. Log rank test was used to compare outcome among different groups of patients.

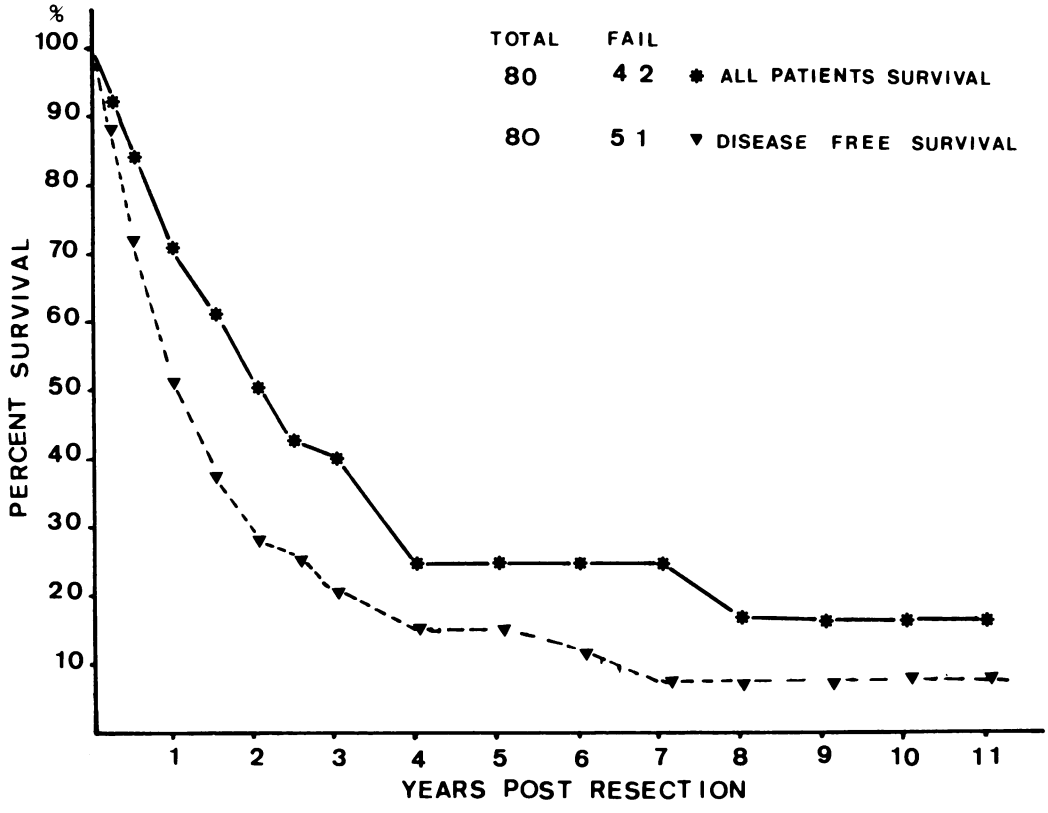

FIG. 1. Overall survival curve (*) and disease free survival curve (▼).

Results

There were no intraoperative deaths in this series. In-hospital mortality rate after liver resection was 5% of the patients and 4.6% of the liver resections since six patients received two resections. Four patients died in hospital: (1) a 44-year-old female died of peritonitis 49 days after liver resection due to the disrupture of an ileocolic anastomosis since the delay between the right colectomy and the right hepatic lobectomy had been too short; (2) a 69-year-old male died of cardiac failure 4 days after an extended right lobectomy; (3) a 55-year-old male died of progressive liver failure 27 days after an extended right lobectomy; and (4) a 69-year-old male died of uncontrollable abdominal bleeding 2 days after a right hepatic lobectomy.

Reversible complications were observed in 10 patients (12.5%): subphrenic abscesses (2 patients), pulmonary emboli (1 patient), septicemia due to infection of I.V. catheter (3 patients), pleural effusion (3 patients), and gastric bleeding (1 patient). All of these were complications observed in patients who had a right lobectomy or an extended right lobectomy. Mean hospital stay in the surviving patients was 16.6 days (range: 7–33 days).

Long-term Results

Thirty-nine patients were alive and 25 were disease-free with a follow-up of 3–180 months at the time the study was completed.

Overall survival and disease-free survival curves are presented in Figure 1. Calculated 2-year, 3-year, and 5-year survival rates were 50.3%, 40.5%, and 24.9%, respectively, including postoperative mortality. Survival curves according to the number of LM resected, to their size, to the Duke's stage of primary adenocarcinoma, and to the delay between colonic resection and the diagnosis of LM are presented, respectively, in Figures 2–6.

There was no difference in survival between patients with solitary LM and either patients with multiple LM or patients with more than four resected LM (Fig. 2). The survival curve of patients with LM smaller than 5 cm was not different than that of patients with LM of more than 5 cm (Fig. 3). The stage of the primary tumor was not a determinant of survival after the resection of the LM (Fig. 4).

No difference in survival was observed either between synchronous and metachronous LM (Fig. 5) or in this second group if the delay was less than 1 year, more than 1 year, or more than 3 years (Fig. 6).

The 22 patients with symptomatic LM had estimated 2-year and 5-year survival rates of 42.8% and 20.4%, respectively. The presence of symptoms was not a significant determinant ($p < 0.05$) of unfavorable prognosis.

Recurrences

Fifty-one patients had recurrent disease during the study. Recurrences occurred during the first 6 months

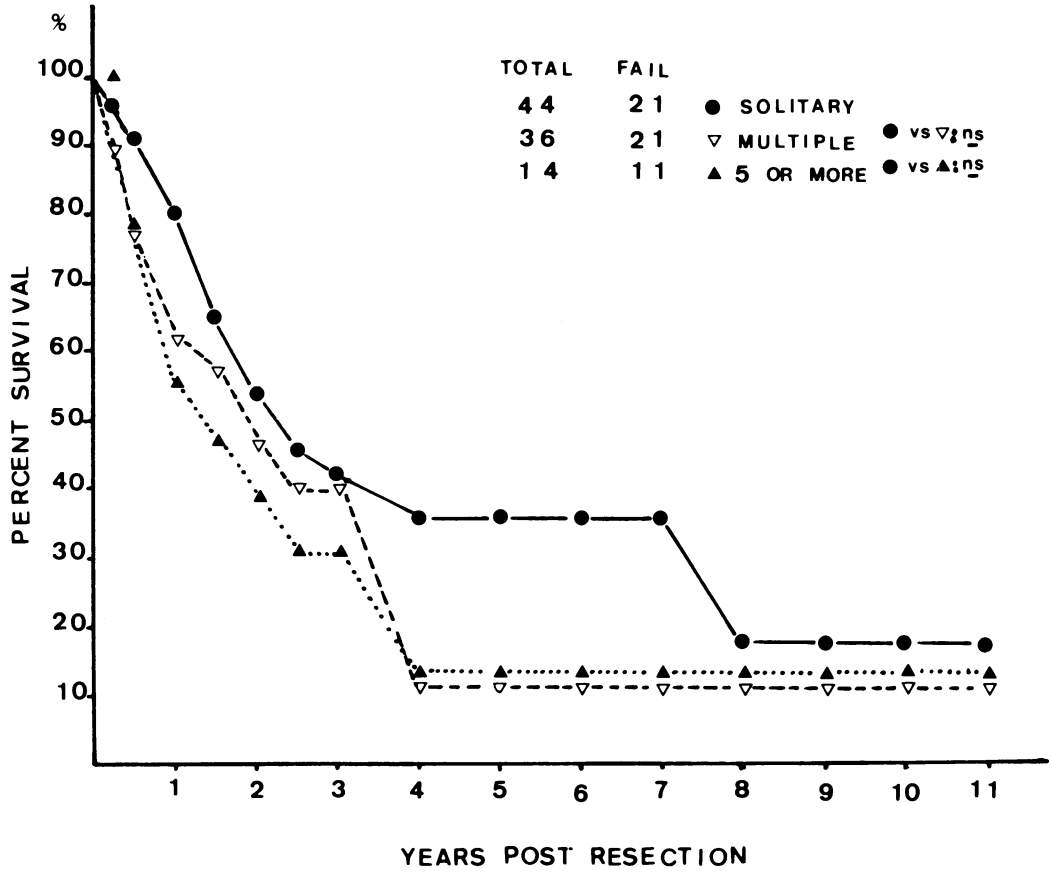

FIG. 2. Survival curves of patients with solitary and multiple LM.

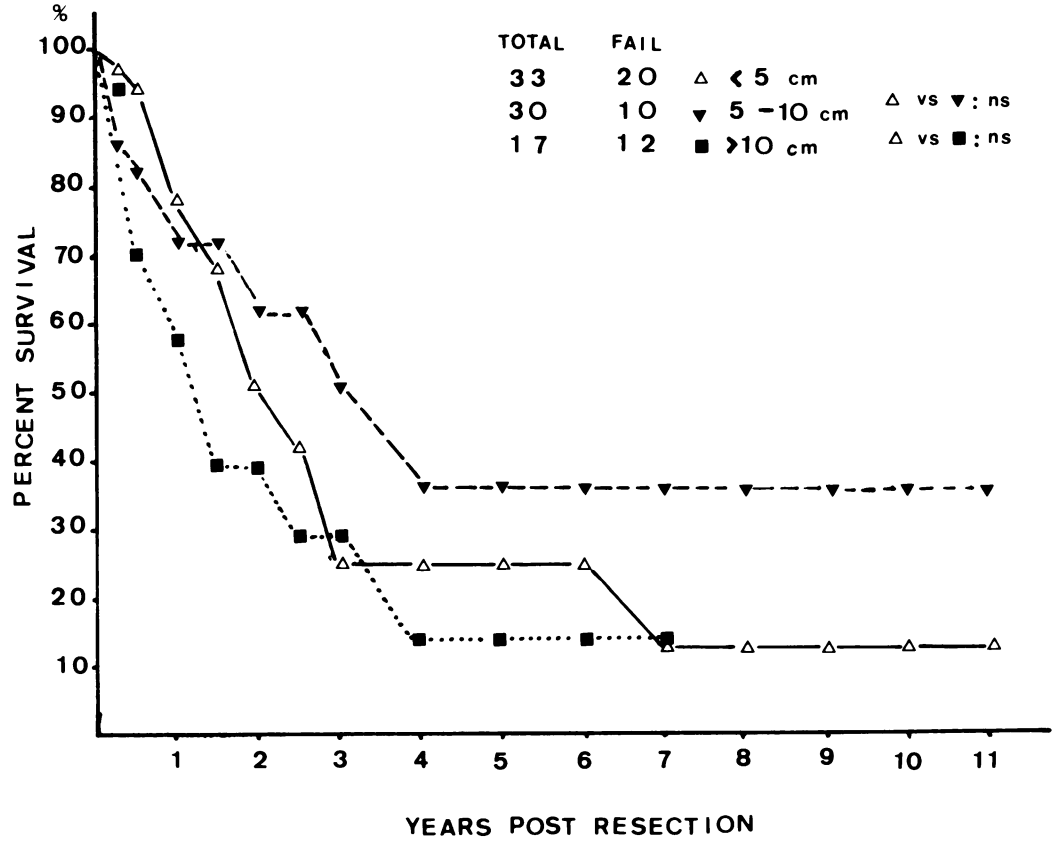

FIG. 3. Survival curves according to the size of resected LM.

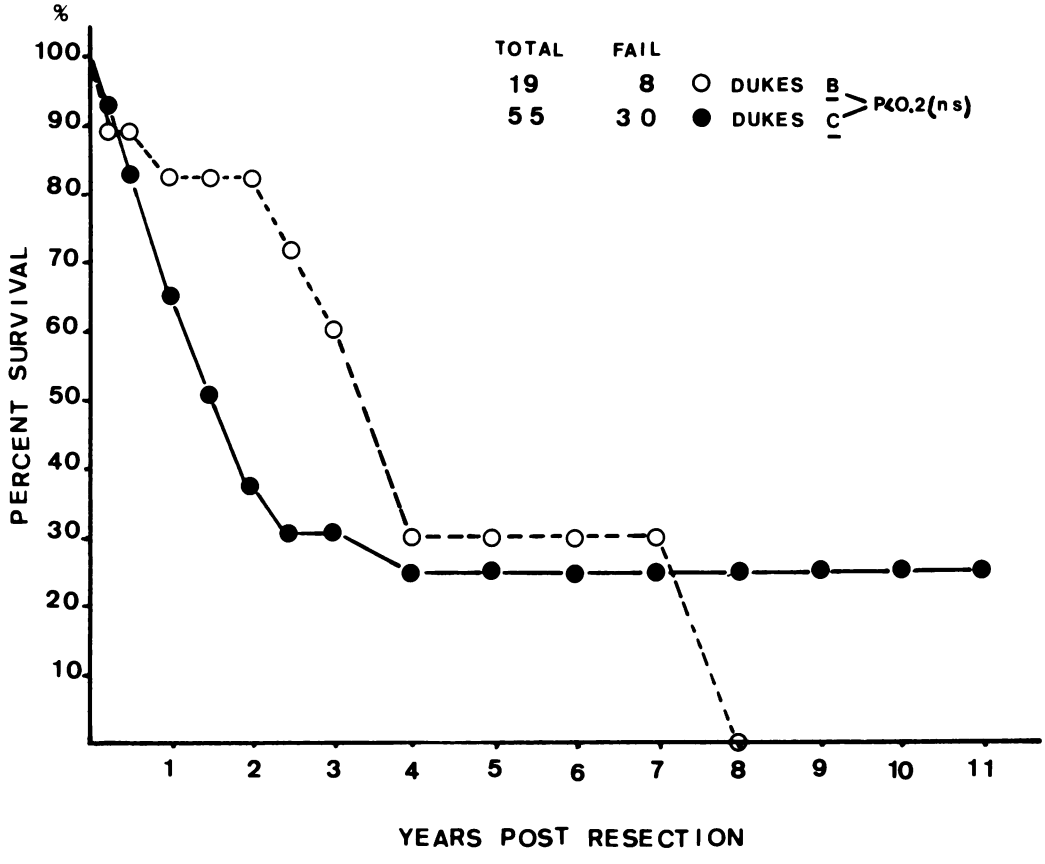

FIG. 4. Survival curves after resection of LM according to the Duke's stage of the primary adenocarcinoma.

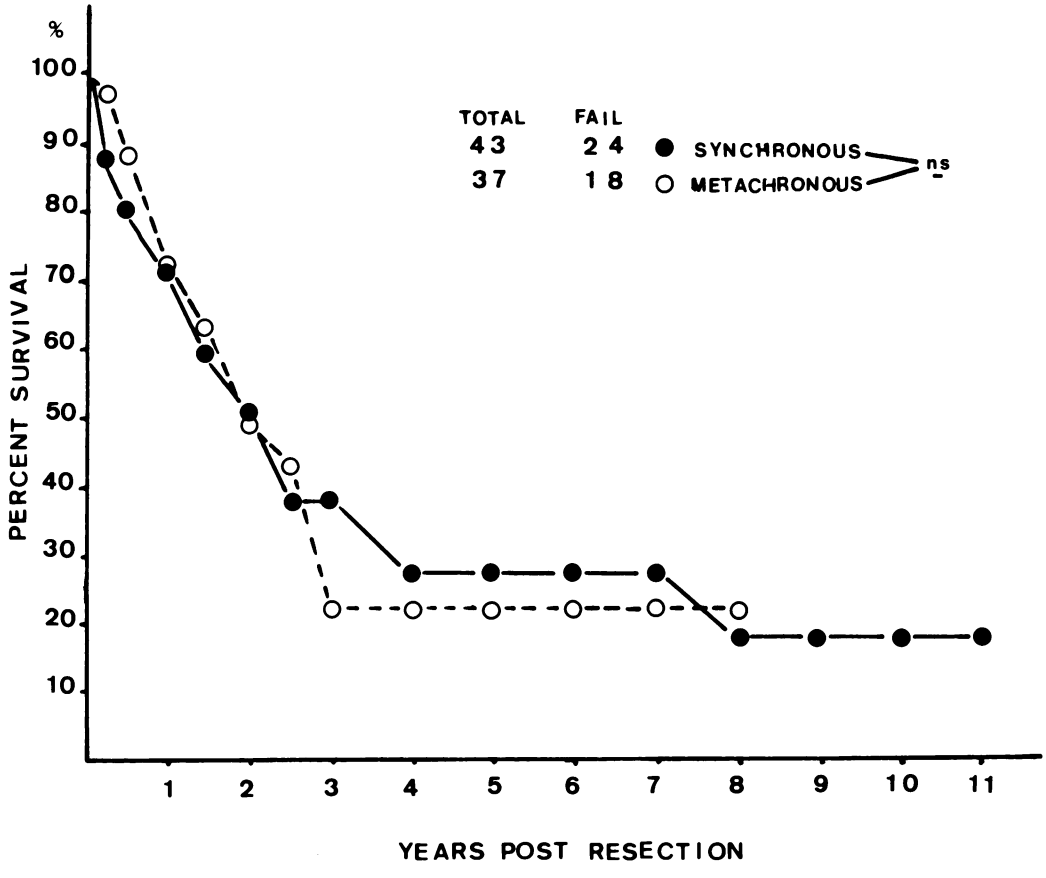

FIG. 5. Survival curves of patients with synchronous and metachronous LM.

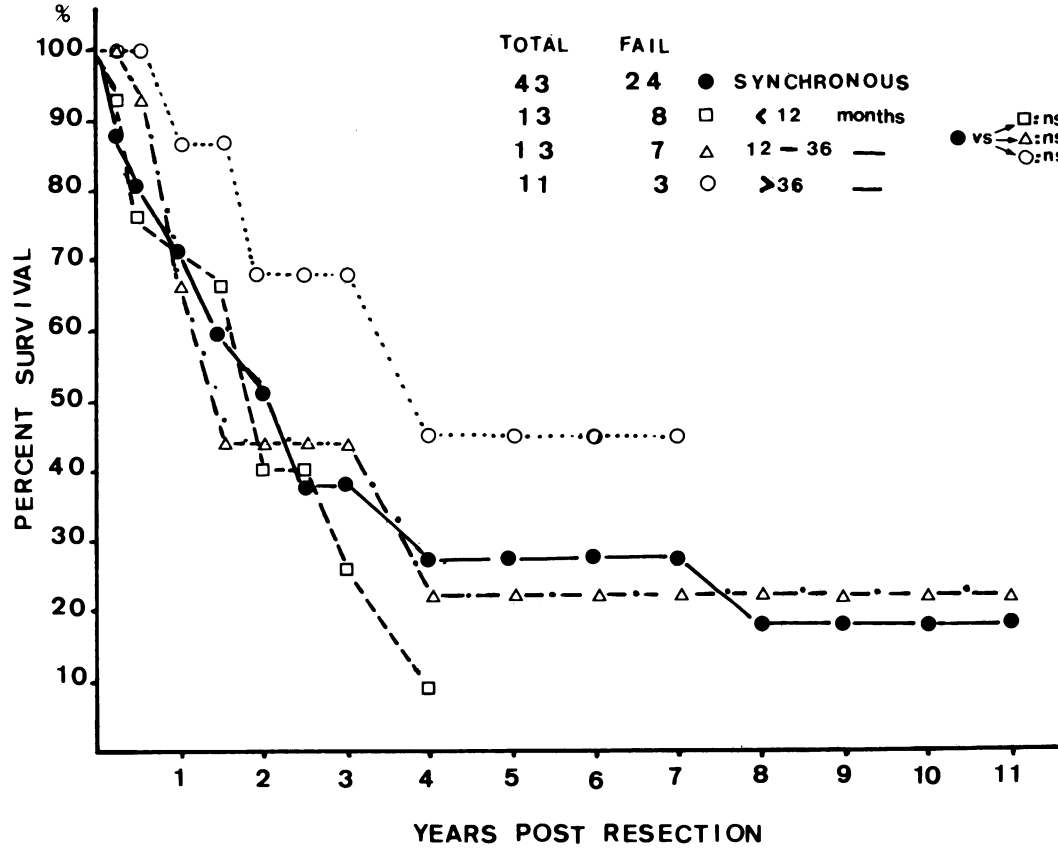

FIG. 6. Survival curves of patients with synchronous and metachronous LM.

after operation in 20 patients and during the next 6 months in 13 patients. Thus, 64.7% of the recurrences occurred during the first year after resection of LM (including patients who had "palliative" resection).

Estimated 12-month, 24-month, and 36-month disease-free survival rates were 50.8%, 27.8%, and 20.3%, respectively (Fig. 1).

The disease recurred in the liver only in 21 patients (41% of recurrences), in extrahepatic sites only in 17 patients (33% of recurrences), and in both locations in 13 patients (26% of recurrences) (Table 4).

One patient had an ovarian carcinoma that required total hysterectomy and intravenous chemotherapy 21 months after colonic resection and 7 months after left liver lobectomy. This patient was alive and doing well 15 months after liver resection.

TABLE 4. *Location of Recurrences Observed During the Study in 51 Patients*

	No. of Patients*
Liver	33 (22)
Local recurrence	11 (10)
Lungs	11 (5)
Peritoneum	6 (6)
Liver pedicule	5 (5)
Bone	4 (4)
Brain	2 (2)
Adrenal glands	1 (0)

* Number of deaths in parentheses.

Surgery for Recurrence

Ten patients had surgery for cancer recurrence after the resection of LM. Four patients were operated on for extrahepatic recurrences: two patients had exploration for unresectable local retroperitoneal recurrence, one patient had a pulmonary resection for a lung metastasis, and another patient had an adrenal metastasis and a pulmonary metastasis resected (Table 5). Six patients had "secondary" LM resected. After the initial liver resection, the disease had recurred in the same liver lobe in three patients and on the opposite lobe in three patients. All those LM remained unilobar at the time of resection (Table 6).

Discussion

Recent years have been marked by an increased interest in the surgical treatment of LM.

These liver deposits are frequent. They are observed in 10–20% of patients operated on for adenocarcinoma of the colon or rectum. In our institution, LM were present in 14% of 3125 patients operated on during an 11-year period for colorectal adenocarcinomas. Furthermore,

TABLE 5. *Second Surgical Procedure for Extrahepatic Recurrences*

Patient	Delay Before Recurrence (Months)	Site	Second Procedure	Survival after Liver Resection (Months)	Current Status
1	14	Local	Exploration	37	Dead
2	8	Local	Exploration	21	Dead
3	15	Lung	Resection	25	Alive
4	65	Lung, Adrenal gland	Resection, Resection	73	Alive

metachronous LM appear later in approximately 10–20% of patients.

Spontaneous prognosis of untreated patients is very poor; most patients die during the first year after discovery of the liver deposits.[2–4]

Only those patients with solitary or unilobar metastases are considered at the current time to be candidates for liver resection, and they represent only a minority of patients with LM, estimated between 5 and 25%.[4–6]

This series of 80 patients is homogeneous since all patients were operated on in the same institution and with the same surgical principles.[7] All LM except four were solitary or unilobar.

The 3-year and 5-year survival rates of 40.5% and 24.9%, respectively, are in the range of recent reports.[4,6,8–10]

It is well known that very few patients survive 5 years when histologically proven LM are left in place.[3,11] Prognosis, although slightly better, remains very poor in patients with solitary or unilobar metastases that would have been resectable but were left in place.[2]

To demonstrate that patients can benefit from resection of LM, operative and hospital mortality must be taken into account when calculating the long-term survival. The risks of wedge resections of small liver nodules are almost null, but in our series the majority of patients required major LM. Our hospital mortality rate of 5% is quite similar to that observed in other series of patients operated on in institutions specialized in liver surgery.[4,8,12,13]

Indeed, the overall benefit of resection of LM would probably be hampered should early mortality rate exceed 10%.

Portal triad occlusion was used in most patients to reduce bleeding during resection.[14] Complete hepatic vascular exclusion proved to reduce the risks of hemorrhage or gaseous embolism due to a tear of hepatic veins and consequently increased the safety during the resection of large tumors or tumors close to the hepatic veins.[15,16]

Analysis of the data clearly show that some patients survive for a long period after resection of LM but others have early hepatic or extrahepatic recurrences. Two thirds of the recurrences observed during the study appeared during the first year and sometimes only a few months after liver surgery, as if the procedure itself had triggered the development of previously infraclinic metastases. This group of patients received little if any benefit from liver surgery, and it would be very useful to isolate criteria that could predict the outcome and thus prevent unuseful liver surgery.

The four patients in whom gross tumor had been left in place, since the liver resection was mainly performed to palliate acute symptoms, were in this group of early recurrences.

However, as opposed to other studies, none of the other factors studied predicted outcome after surgery.[2,8,9,12,13,17,18] Neither the size of metastases as long as they could be completely resected, nor the Duke's stage of the primary cancer or the delay between the diagnosis of the colon cancer and the diagnostic of the LM affected the outcome after resection. Indeed, the longest survivor in this series is alive and free of recurrence more than 15 years after a right colectomy and a right nephrectomy that was required by a Duke's Class C adenocarcinoma extended to the right kidney and associated with a solitary

TABLE 6. *Second Procedure for Hepatic Recurrences*

Patient	First Procedure	Delay Before Recurrence (Months)	Second Procedure	Survival (After First Liver Resection, Months)
1	Wedge resection	15	Extended right	25*
2	Wedge resection	9	Extended right	23†
3	Resection of median lobe	5	Extended right	17‡
4	Wedge resection	40	Right lobectomy	42‡
5	Left lateral segmentectomy	13	Right lobectomy	41†
6	Wedge resection	24	Median lobectomy	40†

* Death.
† Currently alive with recurrence.
‡ Currently alive and without evidence of disease.

LM. The number of LM resected did not affect postoperative outcome, and survival was not different in patients with less than four LM resected or more than four LM resected.

Adjuvant chemotherapy is currently under study in order to try to prevent early recurrences after resection of LM, but no objective data have been obtained yet.[9]

When recurrence after resection of LM appears in extrahepatic sites or when it recurs in the liver but is multifocal, little can be done to prevent progression of the disease. However, in this series two patients had resection of metastases located in the lung or the right adrenal gland. In some patients, LM, although recurring, remain solitary or unilobar and grow slowly, thus allowing secondary resection. Such secondary resections were performed in six patients in this series. In most patients, the first liver resection was a minor resection and the second a major one due to the size of the tumor. Recurring metastases were located as often on the same lobe than on the other lobe of the liver. One patient had a recurrence and died 10 months later and did not benefit from this second liver resection. Another patient has insufficient follow-up, but the four others are alive more than 12 months after the second liver resection. Although follow-up is still short it appears that the results of these secondary resections for recurring metastases may not be very different from the results of primary resections, provided the metastases remain completely resectable.

Indeed, we ignore how far resective surgery for LM from colorectal primaries should go.[1] In most published series, the number of LM resected does not affect prognosis after resection as long as there are no more than four metastases and that they remain unilobar and can be resected by one liver resection.[8] In this series, more than four separate LM were resected in 14 patients. Although the number is small, no obvious difference in survival was observed between these patients and the others.

Attempts to resect bilobar multiple LM, such as a large right metastasis requiring a right lobectomy and a small left deposit requiring a wedge resection, may well have the same outcome than the resection of unilobar LM. This type of combined resections were performed in four patients. The question is to know if an otherwise resectable metastasis should be left in place because a second nodule has been discovered on the other lobe?

It is currently impossible to answer these questions since none of the studied criteria has identified the patients who would benefit the most from resections of LM. However, the increased safety of major liver resections when performed by well-trained surgeons and the use of adjuvant chemotherapy may encourage a more aggressive approach.

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